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L2          1007 SEA FILE=CAPLUS ABB=ON  INSULINOTROPIC
L4          1213 SEA FILE=CAPLUS ABB=ON  (GLP OR GLUCAGON LIKE PEPTIDE)(W)1
L6             1 SEA FILE=REGISTRY ABB=ON  "GLUCAGON-LIKE PEPTIDE 1 (7-37)"/CN
L7             2 SEA FILE=REGISTRY ABB=ON  "GLUCAGON-LIKE PEPTIDE I"/CN OR
                 "GLUCAGON-LIKE PEPTIDE I (HUMAN)"/CN
L8           741 SEA FILE=CAPLUS ABB=ON  L6 OR L7
L9           430 SEA FILE=CAPLUS ABB=ON  (GLP OR GLUCAGON LIKE PEPTIDE)(W)I
L15       517657 SEA FILE=CAPLUS ABB=ON  ACTION
L19      2930200 SEA FILE=CAPLUS ABB=ON  ACTIV?
L20          399 SEA FILE=CAPLUS ABB=ON  L2(8A)(L19 OR L15)
L23          297 SEA FILE=CAPLUS ABB=ON  L2(5A)EFFECT?
L24           86 SEA FILE=CAPLUS ABB=ON  (L4 OR L8 OR L9)(L)(ANALOG? OR DERIV?
                 OR SYNTHETIC?)/OBI
L26        16107 SEA FILE=CAPLUS ABB=ON  INSULIN(2A)SECRET?
L29         2742 SEA FILE=CAPLUS ABB=ON  L26(10A)(IMPROV? OR ENHANC? OR
                 INCREAS? OR EXCEED?)
L31           15 SEA FILE=CAPLUS ABB=ON  (L23 OR L20 OR L29) AND L24

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L32	137	SEA FILE=WPIDS ABB=ON	(GLP OR GLUCAGON LIKE PEPTIDE)(W)(1 OR I)
L33	37	SEA FILE=WPIDS ABB=ON	INSULINOTROPIC
L34	418	SEA FILE=WPIDS ABB=ON	INSULIN (2A)SECRET?
L35	61	SEA FILE=WPIDS ABB=ON	L32(8A)(ANALOG? OR DERIV? OR SYNTHETIC?)
L36	98	SEA FILE=WPIDS ABB=ON	L34(10A)(IMPROV? OR ENHANC? OR INCREAS? OR EXCEED?)
L37	21	SEA FILE=WPIDS ABB=ON	L33(8A)(EFFECT? OR ACTION OR ACTIVIT?)
L38	15	SEA FILE=WPIDS ABB=ON	L35 AND (L36 OR L37)

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=> d que 154

L40	5240	SEA (GLP OR GLUCAGON LIKE PEPTIDE)(W)(1 OR I)
L41	3473	SEA INSULINOTROPIC OR INSULINO TROPIC

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L42        52338 SEA INSULIN(2A) SECRET?
L45         1970 SEA L41(8A)(BETTER OR EFFECT? OR ACTION OR ACTIVIT?)
L47          361 SEA L40(3A)(ANALOG? OR DERIV? OR SYNTHETIC?)
L51         7624 SEA L42(5A)(IMPROV? OR ENHANC? OR INCREAS? OR EXCEED?)
L52         1970 SEA L45(3A)(EFFECT? OR ACTION OR ACTIVIT?)
L54           64 SEA L47 (L) (L51 OR L52)


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PROCESSING COMPLETED FOR L38
L57           45 DUP REM L54 L31 L38 (49 DUPLICATES REMOVED)
                 ANSWERS '1-17' FROM FILE MEDLINE
                 ANSWERS '18-19' FROM FILE JICST-EPLUS
                 ANSWERS '20-22' FROM FILE BIOSIS
                 ANSWER '23' FROM FILE EMBASE
                 ANSWERS '24-32' FROM FILE CAPLUS
                 ANSWERS '33-45' FROM FILE WPIDS

=> d ibib ab 1-23; d ibib ab hitrn 24-32; d ibib ab 33-34; fil hom

L57  ANSWER 1 OF 45     MEDLINE                          DUPLICATE 4
ACCESSION NUMBER:    2000135464     MEDLINE
DOCUMENT NUMBER:     20135464   PubMed ID: 10672909
TITLE:               GLP-1-analogues resistant to degradation by
                     dipeptidyl-peptidase IV in vitro.
AUTHOR:              Gallwitz B; Ropeter T; Morys-Wortmann C; Mentlein R; Siegel
                     E G; Schmidt W E
CORPORATE SOURCE:    Department of Medicine I, St. Josef-Hospital,
                     Ruhr-University of Bochum, Medical School, Gudrunstr,
                     Germany.. baptist.gallwitz@ruhr-uni-bochum.de
SOURCE:              REGULATORY PEPTIDES, (2000 Jan 29) 86 (1-3) 103-11.
                     Journal code: RBB; 8100479. ISSN: 0167-0115.
PUB. COUNTRY:        Netherlands
                     Journal; Article; (JOURNAL ARTICLE)
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Searched by Barb O'Bryen, STIC 308-4291

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000224

AB Glucagon-like peptide-1 (GLP-1) stimulates **insulin secretion** and **improves** glycemic control in type 2 diabetes. In serum the peptide is degraded by dipeptidyl peptidase IV (DPP IV). The resulting short biological half-time limits the therapeutic use of GLP-1. DPP IV requires an intact alpha-amino-group of the N-terminal histidine of GLP-1 in order to perform its enzymatic activity. Therefore, the following GLP- analogues with alterations in the N-terminal position 1 were synthesized: N-methylated- (N-me-GLP-1), alpha-methylated (alpha-me-GLP-1), desamidated- (desamino-GLP-1) and imidazole-lactic-acid substituted GLP-1 (imi-**GLP-1**). All **GLP-1 analogues** except alpha-me-**GLP-1** were hardly degraded by DPP IV in vitro. The **GLP-1 analogues** showed receptor affinity and in vitro biological activity comparable to native GLP-1 in RINm5F cells. GLP-1 receptor affinity was highest for imi-GLP-1, followed by alpha-me-GLP-1 and N-me-GLP-1. Only desamino-GLP-1 showed a 15-fold loss of receptor affinity compared to native **GLP-1**. All **analogues** stimulated intracellular cAMP production in RINm5F cells in concentrations comparable to GLP-1. N-terminal modifications might therefore be useful in the development of long-acting **GLP-1 analogues** for type 2 diabetes therapy.

L57 ANSWER 2 OF 45 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999427896 MEDLINE
DOCUMENT NUMBER: 99427896 PubMed ID: 10499550
TITLE: Glucagon-like peptide-1 regulates the beta cell transcription factor, PDX-1, in insulinoma cells.
AUTHOR: Wang X; Cahill C M; Pineyro M A; Zhou J; Doyle M E; Egan J M
CORPORATE SOURCE: Diabetes Section and Laboratory of Biological Chemistry, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA.
SOURCE: ENDOCRINOLOGY, (1999 Oct) 140 (10) 4904-7.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991012

AB Glucagon-like peptide-1 (GLP-1) **enhances insulin** biosynthesis and **secretion** as well as transcription of the insulin, GLUT2 and glucokinase genes. The latter are also regulated by the PDX-1 homeoprotein. We investigated the possibility that GLP-1 may be having its long-term pleiotropic effects through a hitherto unknown regulation of PDX-1. We found that PDX-1 mRNA level was significantly increased ($p<0.01$) after 2 hours and insulin mRNA level was subsequently increased ($p<0.01$) after 3 hours of treatment with GLP-1 (10 nM) in RIN 1046-38 insulinoma cells. Under these experimental conditions, there was also a 1.6-fold increase in the expression of PDX-1 protein in whole cell and nuclear extracts. Overexpression of PDX-1 in these cells confirmed the finding of the wild type cells such that GLP-1 induced a 2-fold increase in whole cell extracts and a 3-fold increase in nuclear extracts of PDX-1

protein levels. The results of electrophoretic mobility shift experiments showed that PDX-1 protein binding to the A1 element of the rat insulin II promoter was also increased 2 h post treatment with GLP-1. In summary, we have uncovered a previously unknown aspect to the regulation of PDX-1 in beta cells. This has important implications in the physiology of adult beta cells and the treatment of type 2 diabetes mellitus with **GLP -1** or its **analogs**.

L57 ANSWER 3 OF 45 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999451234 MEDLINE
DOCUMENT NUMBER: 99451234 PubMed ID: 10519910
TITLE: Glucagon-like peptide-1, a gastrointestinal hormone with a pharmaceutical potential.
AUTHOR: Holst J J
CORPORATE SOURCE: Department of Medical Physiology, University of Copenhagen, the Panum institute, Blegdamsvej 3, Copenhagen N, DK-2200, Denmark.
SOURCE: CURRENT MEDICINAL CHEMISTRY, (1999 Nov) 6 (11) 1005-17.
Ref: 125
Journal code: C02; 9440157. ISSN: 0929-8673.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991215

AB Glucagon-like peptide-1 (GLP-1) is an insulinotropic hormone secreted from endocrine cells in the gut mucosa in response to meal ingestion. It is an important incretin hormone; mice with a null mutation in the GLP-1 receptor gene develop glucose intolerance. In addition, it inhibits gastrointestinal secretion and motility and is thought to be part of the "ileal brake" mechanism. Perhaps because of the latter actions it inhibits food intake, but intracerebral injection of GLP-1 also inhibits food intake. The **insulinotropic effect** is preserved in patients with type 2 diabetes mellitus, in whom also glucagon secretion is inhibited. Thus upon i.v. GLP-1 infusion blood glucose may be completely normalised. Because its actions are glucose-dependent hypoglycaemia does not develop. However, GLP-1 is metabolised extremely rapidly in vivo, initially by a mechanism that involves the enzyme dipeptidyl peptidase-IV. It is currently being investigated how **GLP-1** or **analogues** thereof can be employed in practical diabetes therapy. Promising solutions include the development of stable analogues and inhibitors of the degrading enzyme.

L57 ANSWER 4 OF 45 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1999340421 MEDLINE
DOCUMENT NUMBER: 99340421 PubMed ID: 10411667
TITLE: Comparison of the effect of native glucagon-like peptide 1 and dipeptidyl peptidase IV-resistant analogues on insulin release from rat pancreatic islets.
AUTHOR: Siegel E G; Scharf G; Gallwitz B; Mentlein R; Morys-Wortmann C; Folsch U R; Schmidt W E
CORPORATE SOURCE: Christian-Albrechts-University of Kiel, Kiel, Germany.
SOURCE: EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, (1999 Jul) 29 (7) 610-4.
Journal code: EN3; 0245331. ISSN: 0014-2972.
PUB. COUNTRY: ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990816

AB BACKGROUND: Glucagon-like peptide 1 (GLP-1) stimulates **insulin secretion** and may **improve** glycaemic control in type 2 diabetes. Therapeutic use is limited by its rapid degradation, primarily by dipeptidyl peptidase IV. MATERIALS AND METHODS: Five **GLP-1 analogues** with alterations at cleavage positions were synthesized according to the Fmoc strategy and tested for metabolic stability by incubation with rat kidney membranes containing dipeptidyl peptidase IV **activity**. Their **insulinotropic effect** was compared in isolated rat pancreatic islets after 24 h maintenance in tissue culture. Ten islets per vial were incubated for 30 min; insulin was measured radioimmunologically. Each **analogue** was compared with **GLP-1** in the same experiment. RESULTS: All analogues were biologically active in isolated islets in the potency order da2d8 = da2 > d2d9 > da2ds8 > desamino. At 16.7 mmol L-1 glucose, **GLP-1** and **GLP-1 analogues** altered as position 2, or 2 and 8 significantly ($P < 0.05$) increased insulin release at 10(-9) mol L-1. N-terminal modification of GLP-1 confers resistance to dipeptidyl peptidase IV degradation in rat kidney membranes in vitro. CONCLUSIONS: The analogues tested are biologically active and resistant to degradation by dipeptidyl peptidase IV. Their greater metabolic stability may help to realize the potential of **GLP-1 analogues** in diabetes therapy.

L57 ANSWER 5 OF 45 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1999199020 MEDLINE
DOCUMENT NUMBER: 99199020 PubMed ID: 10100921
TITLE: Biological activity of GLP-1-analogues with N-terminal modifications.
AUTHOR: Siegel E G; Gallwitz B; Scharf G; Mentlein R; Morys-Wortmann C; Folsch U R; Schrezenmeir J; Drescher K; Schmidt W E
CORPORATE SOURCE: Laboratory for Molecular Gastroenterology and Hepatology, First Department of Medicine, Christian-Albrechts-University, Kiel, Germany.
SOURCE: REGULATORY PEPTIDES, (1999 Feb 5) 79 (2-3) 93-102. Journal code: RBB; 8100479. ISSN: 0167-0115.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990528

AB Glucagon-like peptide-1 (GLP-1) stimulates **insulin secretion** and **improves** glycemic control in type 2 diabetes. In serum the peptide is degraded by dipeptidyl peptidase IV (DPP IV). The resulting short biological half-time limits the therapeutic use of GLP-1. Therefore, various **GLP-1 analogues** with alterations in cleavage positions were synthesized. GLP-1-receptor binding was investigated in RINm5F cells. Biological activity of the **GLP-1 analogues** was investigated in vitro by measuring cAMP production in RINm5F cells. **GLP-1 analogues** with modifications in position 2 were not cleaved by DPP

IV and showed receptor affinity and in vitro biological activity comparable to native **GLP-1**. **Analogues** with alterations in positions 2 and 8, 2 and 9 or 8 and 9 showed a significant decrease in receptor affinity and biological activity. In vivo biological activity was tested in pigs. **GLP-1 analogues** were administered subcutaneously followed by an intravenous bolus injection of glucose. Plasma glucose and insulin were monitored over 4 h. Compared to native **GLP-1**, **analogues** with an altered position 2 showed similar or increased potency and biological half-time. Other **GLP-1 analogues** were less active. Despite the lack of degradation of these **GLP-1 analogues** by DPP IV in vitro, their biological action is as short as that of GLP-1, except for desamino-GLP-1, indicating that other degradation enzymes are important in vivo. Alterations of GLP-1 in positions 8 or 9 result in a loss of biological activity without extending biological half-time.

L57 ANSWER 6 OF 45 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998233302 MEDLINE
DOCUMENT NUMBER: 98233302 PubMed ID: 9571809
TITLE: [Glucagon-like peptide-1--a new hormone and a new drug]. Glukagonlignende peptid-1--et nyt hormon og et nyt laegemiddel.
AUTHOR: Holst J J
CORPORATE SOURCE: Kobenhavns Universitet, Panum Instituttet, Medicinsk Fysiologisk Institut.. Holst@mfi.ku.dk
SOURCE: UGESKRIFT FOR LAEGER, (1998 Apr 13) 160 (16) 2371-7. Journal code: WM8; 0141730. ISSN: 0041-5782.
PUB. COUNTRY: Denmark
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Danish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980611
Last Updated on STN: 20000124
Entered Medline: 19980601

AB Glucagon-like peptide-1 (GLP-1 is an insulinotropic hormone, which is secreted from endocrine cells of the intestinal mucosa in relation to meal ingestion. It plays an important role as an incretin hormone; thus, mice with a null-muation in the gene encoding the GLP-1 receptor are glucose intolerant. In addition, GLP-1 inhibits gastrointestinal secretion and motility and is thought to act as one of the hormones of the "ileal brake". The **insulinotropic effect** of GLP-1 is preserved in patients with non insulin-dependent diabetes mellitus (NIDDM) and, because GLP-1 also inhibits glucagon secretion, it effectively lowers blood glucose in such, and given as an intravenous infusion it may completely normalise blood glucose. Furthermore, because its actions on insulin and glucagon secretion are dependent on the blood glucose levels it will not cause hypoglycemia. Efforts are therefore currently being made to employ **GLP-1** or **analogues** thereof in clinical diabetes treatment, not least because recent investigations have shown that GLP-1, perhaps due to its gastrointestinal actions, is capable of reducing food intake in humans.

L57 ANSWER 7 OF 45 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998192672 MEDLINE
DOCUMENT NUMBER: 98192672 PubMed ID: 9525985
TITLE: Exendin(9-39)amide is an antagonist of glucagon-like peptide-1(7-36)amide in humans.
AUTHOR: Schirra J; Sturm K; Leicht P; Arnold R; Goke B; Katschinski M

CORPORATE SOURCE: Clinical Research Unit for Gastrointestinal Endocrinology and Department of Gastroenterology and Endocrinology, Philipps University, 35033 Marburg, Germany..
schirra@mailer.uni-marburg.de
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1998 Apr 1) 101 (7) 1421-30.
Journal code: HS7; 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980430
Last Updated on STN: 19980430
Entered Medline: 19980423

AB The gastrointestinal hormone, glucagon-like peptide-1(7-36)amide (GLP-1) is released after a meal. The potency of **synthetic GLP -1** in stimulating insulin secretion and in inhibiting glucagon secretion indicates the putative physiological function of GLP-1. In vitro, the nonmammalian peptide, exendin(9-39)amide [ex(9-39)NH2], is a specific and competitive antagonist of GLP-1. This in vivo study examined the efficacy of ex(9-39)NH2 as an antagonist of exogenous GLP-1 and the physiological role of endogenous GLP-1. Six healthy volunteers underwent 10 experiments in random order. In each experiment, a 30-min period of euglycemia was followed by an intravenous infusion of glucose for 150 min that established a stable hyperglycemia of 8 mmol/liter. There was a concomitant intravenous infusion of one of the following: (1) saline, (2) GLP-1 (for 60 min at 0.3 pmol . kg-1 . min-1 that established physiological postprandial plasma levels, and for another 60 min at 0.9 pmol . kg-1 . min-1 to induce supraphysiological plasma levels), (3-5) ex(9-39)NH2 at 30, 60, or 300 pmol . kg-1 . min-1 + GLP-1, (6-8) ex(9-39)NH2 at 30, 60, or 300 pmol . kg-1 . min-1 + saline, (9 and 10) GIP (glucose-dependent insulinotropic peptide; for 60 min at 0.8 pmol . kg-1 . min-1, with saline or ex(9-39)NH2 at 300 pmol . kg-1 . min-1). Each volunteer received each of these concomitant infusions on separate days. ex(9-39)NH2 dose-dependently reduced the **insulinotropic action** of GLP-1 with the inhibitory **effect** declining with increasing doses of GLP-1. ex(9-39)NH2 at 300 pmol . kg-1 . min-1 blocked the **insulinotropic effect** of physiological doses of GLP-1 and completely antagonized the glucagonostatic effect at both doses of GLP-1. Given alone, this load of ex(9-39)NH2 increased plasma glucagon levels during euglycemia and hyperglycemia. It had no effect on plasma levels of insulin during euglycemia but decreased plasma insulin during hyperglycemia. ex(9-39)NH2 did not alter GIP-stimulated insulin secretion. These data indicate that in humans, ex(9-39)NH2 is a potent GLP-1 antagonist without any agonistic properties. The pancreatic A cell is under a tonic inhibitory control of GLP-1. At hyperglycemia, the B cell is under a tonic stimulatory control of GLP-1.

L57 ANSWER 8 OF 45 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 1999069508 MEDLINE
DOCUMENT NUMBER: 99069508 PubMed ID: 9795346
TITLE: A synthetic glucagon-like peptide-1 analog with improved plasma stability.
AUTHOR: Ritzel U; Leonhardt U; Ottleben M; Ruhmann A; Eckart K; Spiess J; Ramadori G
CORPORATE SOURCE: Department of Medicine, Division of Gastroenterology and Endocrinology, University of Gottingen, Gottingen, Germany.
SOURCE: JOURNAL OF ENDOCRINOLOGY, (1998 Oct) 159 (1) 93-102.

Journal code: I1J; 0375363. ISSN: 0022-0795.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990216
Last Updated on STN: 19990216
Entered Medline: 19990129

AB Glucagon-like peptide-1 (GLP-1) is the most potent endogenous insulin-stimulating hormone. In the present study the plasma stability and biological activity of a **GLP-1 analog**, [Ser] **GLP-1**(7-36)amide, in which the second N-terminal amino acid alanine was replaced by serine, was evaluated in vitro and in vivo. Incubation of GLP-1 with human or rat plasma resulted in degradation of native GLP-1(7-36)amide to GLP-1(9-36)amide, while [Ser]GLP-1(7-36)amide was not significantly degraded by plasma enzymes. Using glucose-responsive HIT-T15 cells, [Ser]GLP-1(7-36)amide showed strong **insulinotropic activity**, which was inhibited by the specific GLP-1 receptor antagonist exendin-4(9-39)amide. Simultaneous i.v. injection of [Ser]GLP-1(7-36)amide and glucose in rats induced a twofold higher increase in plasma insulin levels than unmodified GLP-1(7-36)amide with glucose and a fivefold higher increase than glucose alone. [Ser]GLP-1(7-36)amide induced a 1.5-fold higher increase in plasma insulin than GLP-1(7-36)amide when given 1 h before i.v. application of glucose. The **insulinotropic effect** of [Ser]GLP-1(7-36)amide was suppressed by i.v. application of exendin-4(9-39)amide. The present data demonstrate that replacement of the second N-terminal amino acid alanine by serine improves the plasma stability of GLP-1(7-36)amide. The **insulinotropic action** in vitro and in vivo was not impaired significantly by this modification.

L57 ANSWER 9 OF 45 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97193786 MEDLINE
DOCUMENT NUMBER: 97193786 PubMed ID: 9041371
TITLE: Effects of glucagon-like peptide 1 (7-36 amide) on whole-body protein metabolism in healthy man.
AUTHOR: Shalev A; Holst J J; Keller U
CORPORATE SOURCE: Department of Medicine, University Hospital, Basle, Switzerland.
SOURCE: EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, (1997 Jan) 27 (1) 10-6.
Journal code: EN3; 0245331. ISSN: 0014-2972.
PUB. COUNTRY: ENGLAND: United Kingdom
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970609
Last Updated on STN: 20000303
Entered Medline: 19970529

AB The incretin glucagon-like peptide-1 (GLP-1) shows glucose-dependent **insulinotropic activity** and may exert anabolic **effects**. Whole-body protein metabolism was assessed by measuring [1-13C]-leucine kinetics in 13 healthy volunteers during hyperglycaemic clamping with or without pancreatic clamping (somatostatin infusion) in order to differentiate between insulin-mediated and direct GLP-1 effects. During intact pancreatic secretion leucine flux and leucine oxidation rate as parameters of whole-body protein breakdown decreased markedly after 180

min of **synthetic GLP-1** infusion (**GLP -1** vs. placebo: P < 0.003). Indirect calorimetry showed an increase in energy expenditure and CO2 production during GLP-1 administration (P < 0.0005). Plasma insulin increased after 3h of GLP-1 infusion to 1486 +/- 145 pmol L(-1) vs. 185 +/- 12 pmol L(-1) for saline (P < 0.0001). When plasma insulin levels were kept constant (GLP-1 vs. saline, NS) during pancreatic clamping, GLP-1 effects on both protein metabolism and energy expenditure were abolished. Thus, GLP-1 infusion in man exerts protein anticatabolic and thermic effects, which are mediated by GLP-1-induced stimulation of insulin secretion.

L57 ANSWER 10 OF 45 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 96396959 MEDLINE
DOCUMENT NUMBER: 96396959 PubMed ID: 8804062
TITLE: Exchange of W39 by A within the N-terminal extracellular domain of the GLP-1 receptor results in a loss of receptor function.
AUTHOR: Van Eyll B; Goke B; Wilmen A; Goke R
CORPORATE SOURCE: Clinical Research Group for Gastrointestinal Endocrinology, Philipps-University of Marburg, Germany.
SOURCE: PEPTIDES, (1996) 17 (4) 565-70.
Journal code: PA7; 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970124

AB The proglucagon-**derived glucagon-like peptide-1** (GLP-1) secreted by the L-cells exerts an **insulinotropic effect** at pancreatic beta-cells. The GLP-1 receptor belongs to a new subfamily of the superfamily of seven transmembrane, G-protein-coupled receptors (7 TM receptors). We show that a single point mutation within a nonconserved motif of the N-terminal, extracellular domain of the GLP-1 receptor results in a dramatic impairment of receptor function. Thus, substitution of W39 by A or F is followed by a loss of GLP-1 binding. Exchange of K38 with A (mutant K) slightly decreased GLP-1 binding affinity. Replacement of the negatively charged Q37 by K and K38 by A, which is identical with a shift of the positively charged K one position upstream, resulted in a receptor mutant able to bind GLP-1 with higher affinity as the wild-type receptor and mutant K. Therefore, the presence of an imidazol ring structure in the investigated receptor region is necessary for an intact receptor function Furthermore, a positive charge at this location is important for the receptor-ligand interaction.

L57 ANSWER 11 OF 45 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 95113208 MEDLINE
DOCUMENT NUMBER: 95113208 PubMed ID: 7813808
TITLE: Reduction of the incretin effect in rats by the glucagon-like peptide 1 receptor antagonist exendin (9-39) amide.
AUTHOR: Kolligs F; Fehmann H C; Goke R; Goke B
CORPORATE SOURCE: Department of Internal Medicine, Philipps University of Marburg, Germany.
SOURCE: DIABETES, (1995 Jan) 44 (1) 16-9.
Journal code: E8X; 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950217
Last Updated on STN: 19980206
Entered Medline: 19950207

AB Glucagon-like peptide 1 (7-37)/(7-36) amide (**GLP-1**) is **derived** from the intestinal proglucagon processing. It is considered an important insulin-releasing gut hormone. This study uses exendin (9-39) amide as a GLP-1 receptor antagonist to evaluate the contribution of GLP-1 to the incretin effect. Anesthetized rats were challenged by an intraduodenal glucose infusion to evaluate maximally occurring GLP-1 and gastric inhibitory polypeptide (GIP) plasma levels. Maximal immunoreactive (IR) GLP-1 plasma levels amounted to 10 pmol/l (IR-GIP 11 pmol/l). Exendin (9-39) amide abolished the insulin-stimulatory effect of 60 pmol of GLP-1 or of the GLP-1 agonist exendin-4 (0.5 nmol) injected as bolus, respectively. An intravenous bolus injection of 5.94 nmol of exendin (9-39) amide 3 min before enteral glucose infusion grossly reduced the total **insulin secretory** response (by 60%) and significantly **increased** circulating blood glucose levels ($P < 0.05$). In contrast, the GLP-1 antagonist left the insulin response after an intravenous glucose or glucose plus GIP (60 pmol) load unaltered. Our data support the concept that GLP-1 is an important incretin factor. Exendin (9-39) amide is a useful GLP-1 antagonist for in vivo studies.

L57 ANSWER 12 OF 45 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 93307150 MEDLINE
DOCUMENT NUMBER: 93307150 PubMed ID: 8319572
TITLE: Regulation of intestinal proglucagon-derived peptide secretion by glucose-dependent insulinotropic peptide in a novel enteroendocrine loop.
AUTHOR: Roberge J N; Brubaker P L
CORPORATE SOURCE: Department of Physiology, University of Toronto, Ontario, Canada.
SOURCE: ENDOCRINOLOGY, (1993 Jul) 133 (1) 233-40.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930813
Last Updated on STN: 19970203
Entered Medline: 19930803

AB Incretins are intestinal factors that stimulate postprandial insulin secretion in preparation for subsequent rises in plasma levels of ingested nutrients. Glucose-dependent insulinotropic peptide (GIP), a duodenal endocrine peptide, is ideally located for such a function. In contrast, the intestinal proglucagon-**derived** peptide (PGDP), truncated **GLP-1** [GLP-1(7-37) or tGLP-1] is equipotent to GIP in **insulinotropic activity**, but due to its localization in the distal ileum, appears to be poorly situated to fulfill an incretin role in response to direct nutrient stimulation. Despite its distribution, rapid increments in plasma levels of tGLP-1 have been noted in response to nutrient ingestion. We have recently reported that GIP (but not other nutrient-stimulated duodenal endocrine peptides) can stimulate intestinal PGDP secretion in vitro, and therefore hypothesized that GIP might regulate secretion of the intestinal PGDPs, including tGLP-1, in response to nutrient ingestion in vivo in the rat. Placement of either fat or glucose directly into the ileal lumen was demonstrated to significantly stimulate secretion of the intestinal PGDPs ($P < 0.05$), whereas fat or

glucose in the duodenal lumen significantly increased plasma levels of GIP ($P < 0.05$). In addition, however, duodenal fat treatment also increased the secretion of intestinal PGDPs into the circulation ($P < 0.05$), with levels rising to same extent as observed after direct administration of fat into the ileum. The rise in plasma GIP levels in response to duodenal fat treatment occurred slightly before the increments in intestinal PGDP levels, suggesting a relationship between the two peptides. Intravenous infusion of GIP to give concentrations similar to those observed after duodenal fat administration induced a 2-fold increase in plasma levels of intestinal PGDPs that was independent of glycemic levels ($P < 0.05$). No increment in intestinal PGDPs was found in response to infusion of another duodenal endocrine peptide, cholecystokinin. Thus, these data demonstrate a specific effect of GIP to stimulate secretion of the intestinal PGDPs in vivo in the rat. This enteroendocrine loop between the duodenal peptide GIP and the ileal PGDPs may account for some of the early rises in secretion of tGLP-1 observed in response to nutrient ingestion.

L57 ANSWER 13 OF 45 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 92221375 MEDLINE
DOCUMENT NUMBER: 92221375 PubMed ID: 1807008
TITLE: The structure-function relationship of GLP-1 related peptides in the endocrine function of the canine pancreas.
AUTHOR: Ohneda A; Ohneda K; Ohneda M; Koizumi F; Ohashi S; Kawai K; Suzuki S
CORPORATE SOURCE: Health Center, Tohoku University, Sendai.
SOURCE: TOHOKU JOURNAL OF EXPERIMENTAL MEDICINE, (1991 Nov) 165 (3) 209-21.
Journal code: VTF; 0417355. ISSN: 0040-8727.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920529
Last Updated on STN: 19920529
Entered Medline: 19920513

AB In order to clarify the relationship between the structure and function of glucagon-like peptide (GLP) 1 in the endocrine function of the pancreas, the response of insulin and glucagon to various **synthetic GLP-1**-related peptides was investigated in anesthetized dogs. GLP-1-related peptides were administered in a dosage of 400 pmol within 10 min into the pancreatic artery during glucose or arginine infusion and the changes in plasma insulin and glucagon in the pancreatic vein were studied. GLP-1 (7-36) and (7-37), as well as glucagon enhanced insulin release during glucose infusion, whereas neither GLP-1 (1-37), (7-20), (6-37) nor (8-37) stimulated insulin release. The administration of GLP-1 (1-37), (7-36) and (7-37) reduced glucagon release during glucose infusion. When arginine was infused, GLP-1 (7-20), (7-36), (7-37), and glucagon enhanced insulin release. In contrast, glucagon release was increased by the administration of GLP-1 (7-20), (8-37), and (7-37). The present study indicates that histidine at the 7th position of GLP-1 is important in eliciting biological action and that only truncated GLP-1 (7-36), (7-37), and (7-20) showed an **insulinotropic action** as strong as glucagon in dogs. Furthermore, it is suggested that the response of insulin and glucagon to GLP-1-related peptides is dependent on a background condition.

L57 ANSWER 14 OF 45 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 90200928 MEDLINE
DOCUMENT NUMBER: 90200928 PubMed ID: 2156683
TITLE: Glucagon-like peptide-I analogs: effects on insulin

secretion and adenosine 3',5'-monophosphate formation.
AUTHOR: Gefel D; Hendrick G K; Mojsov S; Habener J; Weir G C
CORPORATE SOURCE: Joslin Diabetes Center, Boston, Massachusetts 02215.
CONTRACT NUMBER: AM-30834 (NIADDK)
DK-35449 (NIDDK)
DK-P30-36836 (NIDDK)
+
SOURCE: ENDOCRINOLOGY, (1990 Apr) 126 (4) 2164-8.
Journal code: EGZ; 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199004
ENTRY DATE: Entered STN: 19900601
Last Updated on STN: 19900601
Entered Medline: 19900430

AB Glucagon-like peptide 1-(7-37) [GLP-I-(7-37)] is a 31-amino acid hormone which may have an important role in the regulation of insulin secretion, It is processed from preproglucagon and found in the pancreas, brain, and, in highest quantity, intestine. In previous studies we found that GLP-I-(7-37) is a potent insulin secretagogue, and its effect was indistinguishable from that of GLP-I-(7-36) amide at concentrations of 10(-11) M. Herein we report **insulinotropic effects** of additional **GLP-I analogs**. **GLP-I**-(7-34) had no stimulatory effect on insulin release at 10(-10) M, but had a partial effect at 10(-9) M and was as active as GLP-I-(7-37) at 10(-8) M. GLP-I-(7-33) had no effect at any concentration tested. GLP-I-(8-37) caused no significant effect on insulin release at 10(-9) and 10(-8) M, but did have an effect at the high concentration of 10(-7) M. Similar results were found with cAMP formation in the beta TC1 line. In this system GLP-I-(7-34) was less potent than GLP-I-(7-37) at a concentration of 5 x 10(-9) M. GLP-I-(7-33) had only about 0.1% the potency of GLP-I-(7-37); thus, there is good agreement between cAMP formation in the beta-cell line and insulin secretion from the perfused pancreas experiments. We conclude that histidine in the 7 position in the N-terminus of GLP-I-(7-37) is crucial for cAMP formation and insulin secretion, and that removal of the last three C-terminus residues of GLP-I-(7-37) results in only partial loss of activity; the residue in the 34 position is, however, essential for the **insulinotropic action**.

L57 ANSWER 15 OF 45 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 89170155 MEDLINE
DOCUMENT NUMBER: 89170155 PubMed ID: 3069410
TITLE: Glucagon-like peptide-1 (7-36 amide): a potent glucagonostatic and insulinotropic hormone.
AUTHOR: Matsuyama T; Komatsu R; Namba M; Watanabe N; Itoh H; Tarui S
CORPORATE SOURCE: Division of Clinical Laboratory, National Cardiovascular Center Hospital, Osaka, Japan.
SOURCE: DIABETES RESEARCH AND CLINICAL PRACTICE, (1988 Oct 14) 5 (4) 281-4.
Journal code: EBI; 8508335. ISSN: 0168-8227.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198905
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19900306

Entered Medline: 19890502

AB Glucagon-like peptide-1 (GLP-1) (1-37) and the fraction **derived** from it, **GLP-1** (7-36 amide), are peptides encoded by the preproglucagon gene and possibly co-secreted with enteroglucagon. When added at a 25-nM concentration, GLP-1 (7-36 amide) decreased the release of glucagon from the perfused rat pancreas from 68.5 +/- 9.0 pg/ml to 41.5 +/- 11.5 pg/ml at 2 min in the presence of 11.2 mM glucose (P less than 0.01), and from 196.0 +/- 32.5 pg/ml to 87.0 +/- 23.5 pg/ml at 5 min in the presence of 2.8 mM glucose (P less than 0.05). Insulin levels increased from 12.6 +/- 3.0 microU/ml to 48.9 +/- 14.0 microU/ml at 10 min in the presence of 11.2 mM glucose (P less than 0.05) and from 2.0 +/- 0.4 microU/ml to 8.2 +/- 2.3 microU/ml at 2 min in the presence of 2.8 mM glucose (P less than 0.05). Glucagon and insulin release were not affected significantly by GLP-1 (1-37), irrespective of glucose concentration. We suggest that GLP-1 (7-36 amide) rather than enteroglucagon may be the true physiologic gut hormone and that it may act as 'incretin' in the enteroinsular axis. We suggest further that the glucagonostatic and **insulinotropic activities** of this peptide are unique and might be important in islet-cell function.

L57 ANSWER 16 OF 45 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 86056688 MEDLINE
DOCUMENT NUMBER: 86056688 PubMed ID: 3905480
TITLE: Glucagon-like peptide-1 but not glucagon-like peptide-2 stimulates insulin release from isolated rat pancreatic islets.
AUTHOR: Schmidt W E; Siegel E G; Creutzfeldt W
SOURCE: DIABETOLOGIA, (1985 Sep) 28 (9) 704-7.
Journal code: E93; 0006777. ISSN: 0012-186X.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198601
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860121

AB Glucagon-like peptide-1 and glucagon-like peptide-2 are encoded by the m-RNA of pancreatic preproglucagon. They show high conservation in different species and substantial sequence homology to glucagon. Because no definite biological activity of these peptides has been reported, we investigated the effect of **synthetic** C-terminally amidated **glucagon-like peptide-1** [1-36] and **synthetic** human glucagon-like peptide-2 [1-34] with a free C-terminus on insulin release from isolated precultured rat pancreatic islets in the presence of glucose. Glucagon-like peptide-1 stimulates insulin release at 10 and 16.7 mmol/l glucose in a dose-dependent manner. Significant stimulation starts at 2.5 nmol/l in the presence of 10 mmol/l glucose and near maximal release is observed at 250 nmol/l, with approximately 100% increase over basal at both glucose concentrations. The peptide reaches 63% of the maximal stimulatory effect of glucagon. No stimulation occurs in the presence of 2.8 mmol/l glucose. Glucagon-like peptide-2 has no effect on insulin secretion at any glucose concentration tested. It is concluded that glucagon-like peptide-1, in contrast to glucagon-like peptide-2, exhibits a glucose-dependent **insulinotropic action** on isolated rat pancreatic islets similar to that of glucagon and gastric inhibitory polypeptide.

L57 ANSWER 17 OF 45 MEDLINE
ACCESSION NUMBER: 2000280282 MEDLINE
DOCUMENT NUMBER: 20280282 PubMed ID: 10820647

TITLE: Recent developments and emerging therapies for type 2 diabetes mellitus.
AUTHOR: Evans A J; Krentz A J
CORPORATE SOURCE: Department of Diabetes and Endocrinology, Southampton General Hospital, England.
SOURCE: DRUGS IN R&D, (1999 Aug) 2 (2) 75-94. Ref: 106
Journal code: DIY; 100883647. ISSN: 1174-5886.
PUB. COUNTRY: New Zealand
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000801

AB Most patients with type 2 (non-insulin-dependent) diabetes mellitus require pharmacotherapy, initially as monotherapy and subsequently in combination, as adjuncts to diet and exercise. Exogenous insulin is ultimately required in a substantial proportion, reflecting the progressive natural history of the disease. Sulphonylureas and biguanides have been employed for over 4 decades as oral antidiabetic agents, but they have a limited capacity to provide long term glycaemic control and can cause serious adverse effects. Thus, more efficacious and tolerable antidiabetic agents are required. Recent years have witnessed the introduction of agents with novel modes of action, that is, the alpha-glucosidase inhibitors acarbose and miglitol (which reduce postprandial hyperglycaemia) and the first of the thiazolidinedione insulinsensitising drugs--troglitazone and rosiglitazone. Although the former has been withdrawn in some countries due to adverse effects, another 'glitazone' pioglitazone is expected to be approved in the near future. Other recently introduced drugs include glimepiride and the meglitinide **insulin secretagogue**, repaglinide.
Attention is also focusing **increasingly** on combination therapy using insulin together with sulphonylureas, metformin or troglitazone. Rapid-acting insulin analogues are now being used as alternatives to conventional insulins; their role in the management of type 2 diabetes mellitus is presently uncertain but reports of a reduced frequency of hypoglycaemia are encouraging. The development of new drugs aims to counter the principal metabolic defects of the disorder, respectively, relative insulin deficiency and insulin resistance. Novel classes of rapid-acting secretagogues under evaluation include the morphilinoguanide BTS 67582 and the meglitinides mitiglinide (KAD 1229) and senaglinide (A-4166). Succinate ester derivatives represent a potential novel approach to improving beta-cell function through **enhancement** of **insulin** biosynthesis and **secretion**. **Enhancement** of nutrient-induced **insulin secretion** is a mechanism with several putative targets within the beta-cell; potentiators of insulin secretion include **glucagon-like peptide-1** and its **analogues**, phosphodiesterase inhibitors and the imidazoline derivative PMS 812 (S 21663). The amylin agonist pramlintide slows gastric emptying and suppression of glucagon secretion. Non-thiazolidinedione insulin-sensitising agents include the gamma-receptor agonist G 1262570X (GG 570) and D-chiro-inositol. Insulin analogues with prolonged action and inhaled insulin preparations are also under investigation. Insulin-mimetic agents include organic vanadium compounds. Whether newer agents will offer clinically relevant efficacy and tolerability advantages over existing therapies remains to be determined.

L57 ANSWER 18 OF 45 JICST-EPlus COPYRIGHT 2001 JST DUPLICATE 19
ACCESSION NUMBER: 900463198 JICST-EPlus
TITLE: Radioimmunoassay for glucagon-like peptide-1 in human plasma using N-terminal and C-terminal directed antibodies: A physiologic insulinotropic role of GLP-1 (7-36 amide).
AUTHOR: TAKAHASHI H; MANAKA H; SUDA K; FUKASE N; TOMINAGA M; SASAKI H
KAWAI K
OHASHI S
CORPORATE SOURCE: Yamagata Univ. School of Medicine, Yamagata, JPN
Univ. Tsukuba, Ibaraki, JPN
Research Inst. Polymers and Textiles, Ibaraki, JPN
SOURCE: Biomed Res, (1990) vol. 11, no. 2, pp. 99-108. Journal Code: Z0236B (Fig. 6, Tbl. 1, Ref. 31)
ISSN: 0388-6107
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New
AB To investigate physiologic function of glucagon-like peptide-1 (GLP-1)(7-36 amide), a method for estimating the level of truncated GLP-1 in human plasma was developed by means of radioimmunoassay (RIA) systems using C-terminal and N-terminal directed antibodies. The antisera were raised in three rabbits after emulsification of **synthetic** human **GLP-1** (1-36 amide) or human GLP-1 (7-36 amide) with 50% polyvinylpyrrolidone. The selected antisera did not cross-react with any other peptides of glucagon family. Using various **synthetic** fragments of human **GLP-1**, R1043 antiserum was found to be directed against the N-terminus and R2337 antiserum against the C-terminus of GLP-1. In radioimmunoassays using these two antisera, the detection limit was 24pmol/l for both assays. Accurate determination of GLP-1 levels in human plasma required ethanol extraction. The optimal recovery was obtained with 67% ethanol (final concentration) for both assays. The fasting plasma levels of GLP-1 in 83 healthy subjects were 22.6.+-.1.9pmol/l for R1043 assay and 71.5.+-.3.3pmol/l for R2337 assay, respectively. After ingestion of 75g glucose in 10 healthy subjects GLP-1 IR measured with R1043 assay decreased gradually for 2h, whereas the values measured with R2337 assay rose to 84.4.+-.6.4pmol/l at 30min and sustained high for 2h. On gelfitration of serum obtained 30min after oral glucose loading, truncated GLP-1 fraction increased but full sequence GLP-1 fraction decreased. These results together with our previous report using perfused rat pancreas, suggest that truncated GLP-1 has a Potent **insulinotropic effect**. (author abst.)

L57 ANSWER 19 OF 45 JICST-EPlus COPYRIGHT 2001 JST DUPLICATE 21
ACCESSION NUMBER: 890603799 JICST-EPlus
TITLE: Glucagon-like peptide-1: Synthetic aproach.
AUTHOR: YANAIHARA C; KUROKAWA N
SUZUKI M; ISHIKAWA J; YANAIHARA N
CORPORATE SOURCE: Osaka Univ., Osaka, JPN
Univ. Shizuoka Shool of Pharmaceutical Sciences, Shizuoka, JPN
SOURCE: Biomed Res, (1988) vol. 9, no. Suppl 3, pp. 225-228. Journal Code: Z0236B (Fig. 5, Ref. 5)
ISSN: 0388-6107
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New
AB Attention was directed to the primary structure of the carboxyl-terminal portion of glucagon-like peptide-1(GLP-1) which is still ambiguous in

terms of its endogenous form(s) of physiological significance. GLP-1-related peptides shortened in amino or/and carboxyl-terminal portions of GLP-1(1-37) were synthesized and their **insulinotropic** potencies were assessed by the stimulating **effect** on 13.9 mM glucoseinduced insulin release from isolated perfused rat pancreas. The **synthetic** peptides include **GLP-1** (1-37),(1-36),(1-35),(7-37),(7-36),(7-35),(7-22) and (9-22). At a 10-8M concentration, **synthetic GLP-1**(7-35) was the most potent among the eight related peptides examined and exhibited an insulin release enhancing effect over 3-fold stronger than that of 10-8M glucagon. The results support that GLP-1(7-35) can not be excluded from the candidate forms for endogenous GLP-1 related peptide(s).(author abst.)

L57 ANSWER 20 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 2001:388148 BIOSIS
DOCUMENT NUMBER: PREV200100388148
TITLE: The entero-insular axis in type 2 diabetes - incretins as therapeutic agents.
AUTHOR(S): Creutzfeldt, W. (1)
CORPORATE SOURCE: (1) Zentrum Innere Medizin, Klinikum der Universitaet, Robert-Koch-Str. 40, D-37075, Goettingen Germany
SOURCE: Experimental and Clinical Endocrinology & Diabetes, (2001) Vol. 109, No. Suppl. 2, pp. S288-S303. print. ISSN: 0947-7349.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The search for intestinal factors regulating the endocrine secretion of the pancreas started soon after the discovery of secretin, i.e. nearly 100 years ago. Insulinotropic factors of the gut released by nutrients and stimulating insulin secretion in physiological concentrations in the presence of elevated blood glucose levels have been named incretins. Of the known gut hormones only gastric inhibitory polypeptide (GIP) and glucagon-like polypeptide-1 (GLP-1 (7-36) amide) fulfill this definition. - The incretin effect (i.e. the ratio between the integrated insulin response to an oral glucose load and an isoglycaemic intravenous glucose infusion) is markedly diminished in patients with type 2 diabetes mellitus, while the plasma levels of GIP and GLP-1 and their responses to nutrients are in the normal range. Therefore, a reduced responsiveness of the islet B-cells to incretins has been postulated. This insensitivity of the diabetic B-cells towards incretins can be overcome by supraphysiological (pharmacological) concentrations of GLP-1 (7-36), however not of GIP. Accordingly, fasting and postprandial glucose levels can be normalized in patients with type 2 diabetes by infusions of GLP-1 (7-36). Further studies reviealed that this is partially due to the fact that GLP-1 (7-36) - in addition to its **insulinotropic effect** - also inhibits glucagon secretion and delays gastric emptying. These three antidiabetic effects qualify GLP-1 (7-36) as an interesting therapeutic tool, mainly for type 2 diabetes. However, because of its short plasma half life time natural GLP-1 (7-36) is not suitable for subcutaneous application. At present methods are being developed to improve the pharmacokinetics of GLP-1 by inhibition of the cleaving enzyme dipeptidyl peptidase IV (DPP-IV) or by synthesis of DPP-IV resistant **GLP-1 analogues**. Also naturally occurring **GLP-1 analogues** (for instance exendin-4) with a much longer half life time than GLP-1 (7-36) are being tested. - Thus, after 100 years of speculations and experimentations, incretins and their analogues are emerging as new antidiabetic drugs.

L57 ANSWER 21 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 2001:324027 BIOSIS

DOCUMENT NUMBER: PREV200100324027
TITLE: Amphibian glucagon family peptides: Potent metabolic regulators in fish hepatocytes.
AUTHOR(S): Mommsen, Thomas P. (1); Conlon, J. Michael; Irwin, David M.
CORPORATE SOURCE: (1) Department of Biochemistry and Microbiology, University of Victoria, Victoria, BC, V8W 3P6: tpmom@uvic.ca Canada
SOURCE: Regulatory Peptides, (15 June, 2001) Vol. 99, No. 2-3, pp. 111-118. print.
ISSN: 0167-0115.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Peptides **analogous** to **glucagon-like peptide-1** (GLP-1) have been isolated from amphibian pancreas and intestine, and their amino acid sequences and cDNA structures elucidated. Just like their mammalian counterpart, these peptides are potent insulinotropins in mammalian pancreatic cells. We show here that these peptides also exert strong glycogenolytic actions when applied to dispersed fish hepatocytes. We compared the potencies of three synthetic GLP-1s from Xenopus laevis and two native GLP-1s from Bufo marinus in the activation of glycogenolysis in the hepatocytes of a marine rockfish (Sebastes caurinus) and two freshwater catfish (Ameiurus nebulosus and A. melas), and demonstrated their effectiveness in increasing the degree of phosphorylation of glycogen phosphorylase. We also compared the glycogenolytic potency of the peptides with those of human GLP-1 and glucagons from human and B. marinus. Sensitivity to these peptides is species-specific, with the rockfish responding at lower concentrations to GLP-1s and the two catfish reacting better to glucagons. However, the relative potency of the amphibian GLP-1s and glucagons is similar in the three species. Xenopus GLP-1C (xGLP-1C) is consistently more potent than xGLP-1B, while xGLP-1A displays the smallest activation of glycogenolysis. Similarly, Bufo GLP-1(32)-the peptide with the highest amino acid sequence identity to xGLP-1C-always shows a higher potency than Bufo GLP-1(37), which is closely related to xGLP-1B. The relative hierarchy of these glycogenolytic GLP-1s differs from their ranking as insulinotropins in mammalian beta-cells. In the rockfish system, Bufo glucagon-36, a C-terminally extended glucagon, is more potent than the shorter bovine glucagon and Bufo glucagon-29 in the activation of glycogenolysis; when tested in A. nebulosus hepatocytes, bovine and amphibian glucagons are equipotent. Amphibian GLP-1s and glucagons activate glycogenolysis in fish hepatocytes through increased phosphorylation of glycogen phosphorylase, implying involvement of the adenylyl cyclase/protein kinase A system in signal transduction. We conclude that the broad physiological effectiveness of GLP-1 has been retained throughout vertebrate evolution, and that both **insulinotropic activity** and glycogenolytic actions belong to the repertoire of GLP-1.

L57 ANSWER 22 OF 45 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:285363 BIOSIS
DOCUMENT NUMBER: PREV200100285363
TITLE: DNA encoding insulinotropic hormone.
AUTHOR(S): Habener, Joel F. (1)
CORPORATE SOURCE: (1) Newton Highlands, MA USA
ASSIGNEE: The General Hospital Corporation
PATENT INFORMATION: US 6162907 December 19, 2000
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 19, 2000) Vol. 1241, No. 3, pp. No Pagination. e-file.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

AB **Derivatives** of **glucagon-like peptide** I (GLP-1) and especially GLP-1(7-36) have been found to have **insulinotropic activity**. The invention pertains to the use of GLP-1(7-36) for the treatment of type II diabetes mellitus.

L57 ANSWER 23 OF 45 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998205722 EMBASE
TITLE: Treatment of type 2 diabetes with glucagonlike peptide 1.
AUTHOR: Hoist J.J.
CORPORATE SOURCE: J.J. Hoist, Department of Medical Physiology, University of Copenhagen, Panum Institute, Blegdamsvej 3, DK-2200 Copenhagen N, Denmark
SOURCE: Current Opinion in Endocrinology and Diabetes, (1998) 5/2 (108-115).
Refs: 78
ISSN: 1068-3097 CODEN: CENDES
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Glucagonlike peptide 1 (GLP-1) is an insulinotropic hormone secreted from endocrine cells in the gut mucosa in response to meal ingestion. It is an important incretin hormone; mice with a null mutation in the GLP-1 receptor gene develop glucose intolerance. In addition, it inhibits gastrointestinal secretion and motility and is thought to be part of the 'ileal brake' mechanism. Perhaps because of the latter actions it inhibits food intake, but intracerebral injection of GLP-1 also inhibits food intake. The **insulinotropic effect** is preserved in patients with type 2 diabetes mellitus, in whom glucagon secretion is also inhibited. Thus, upon intravenous GLP-1 infusion, the blood glucose level may be completely normalized. Because its actions are glucose dependent, hypoglycemia does not develop. It is currently being investigated how **GLP-1** or **analogues** thereof can be employed in practical diabetes therapy.

L57 ANSWER 24 OF 45 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
ACCESSION NUMBER: 2000:790326 CAPLUS
DOCUMENT NUMBER: 133:345167
TITLE: Metabolic intervention with **GLP-1** or its biologically active **analogues** to improve the function of the ischemic and reperfused brain
INVENTOR(S): Coolidge, Thomas R.; Ehlers, Mario R. W.
PATENT ASSIGNEE(S): Bionebraska, Inc., USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066142	A2	20001109	WO 2000-US11652	20000501

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,

CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-303016 A 19990430

AB It has now been discovered that GLP-1 treatment after acute stroke or hemorrhage, preferably i.v. administration, can be an ideal treatment because it provides a means for optimizing **insulin secretion**, **increasing** brain anabolism, **enhancing** insulin effectiveness by suppressing glucagon, and maintaining euglycemia or mild hypoglycemia with no risk of severe hypoglycemia.

IT **89750-14-1, Glucagon-like peptide I 89750-14-1D, Glucagon-like peptide I, analogs**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metabolic intervention with **GLP-1** or biol. active **analogs** to improve function of ischemic and reperfused brain)

IT **87805-34-3, Glucagon-like peptide I** (human)
RL: PRP (Properties)
(unclaimed protein sequence; metabolic intervention with **GLP-1** or its biol. active **analogs** to improve the function of the ischemic and reperfused brain)

L57 ANSWER 25 OF 45 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
ACCESSION NUMBER: 1999:566074 CAPLUS
DOCUMENT NUMBER: 131:194807
TITLE: Insulinotropic N-terminally truncated **GLP-1** lipophilic **derivatives** with protracted action
INVENTOR(S): Knudsen, Liselotte Bjerre; Huusfeldt, Per Olaf
PATENT ASSIGNEE(S): Novo Nordisk A/s, Den.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9943705	A1	19990902	WO 1999-DK81	19990225
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9926105	A1	19990915	AU 1999-26105	19990225
EP 1056774	A1	20001206	EP 1999-906075	19990225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

PRIORITY APPLN. INFO.: DK 1998-264 A 19980227
DK 1998-509 A 19980408
WO 1999-DK81 W 19990225

OTHER SOURCE(S): MARPAT 131:194807
AB The present invention relates to N-terminally truncated derivs. of human glucagon-like peptide-1 (GLP-1) and analogs thereof having a protracted profile of action, as well as the use of such derivs. in pharmaceutical compns. for the treatment of obesity, insulin dependent or non-insulin dependent diabetes mellitus. The GLP-1 derivs. have a lipophilic substituent attached to at least one amino acid residue.
REFERENCE COUNT: 7
REFERENCE(S):
(1) Eli Lilly And Company; EP 0699686 A2 1996 CAPLUS
(2) Knudsen, L; European Journal of Pharmacology 1996, V318, P429 CAPLUS
(3) London Health Association; WO 9531214 A1 1995 CAPLUS
(5) Novo Nordisk AS; WO 9629342 A1 1996 CAPLUS
(6) Novo Nordisk AS; WO 9731943 A1 1997 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 26 OF 45 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:822535 CAPLUS
DOCUMENT NUMBER: 133:345168
TITLE: Protein kinase B/Akt activator-based method for promotion of cell growth of insulin-secreting cells, and use in treatment of disorders of carbohydrate metabolism
INVENTOR(S): Horsch, Dieter
PATENT ASSIGNEE(S): Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19921537	A1	20001123	DE 1999-19921537	19990511

AB A method is provided for the therapy of disturbances of carbohydrate metab. by **improvement** of the cellular function of **insulin-secreting** .beta. cells by inducing their proliferation and preventing their premature programmed cell death, thereby increasing the quantity of the body's own insulin, which can be released with increased blood sugar level. A preferred method comprises the administration of effectors which activate protein kinase B/Akt in the insulin-secreting .beta. cells. Preferred effectors include GLP-1, GIP, exendin-4, GLP-1 receptor agonists, GIP receptor agonists, and their pharmacol. salts and derivs. The invention also provides a method for isolating substances which promote growth of insulin-secreting cells by activation of PKB/Akt and prevent premature cell death.
IT **89750-14-1D**, Glucagon-related peptide 1, **derivs.**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein kinase B/Akt activator-based method for promotion of cell growth of insulin-secreting cells, and use in treatment of disorders of carbohydrate metab.)
REFERENCE COUNT: 4
REFERENCE(S):
(1) Anon; WO 0007617 A1 CAPLUS
(2) Anon; WO 9906059 A2 CAPLUS
(3) Anon; WO 9944598 A2 CAPLUS
(4) Edvell, A; Endocronology 1999, V140(2), PS778

L57 ANSWER 27 OF 45 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:172415 CAPLUS
DOCUMENT NUMBER: 130:277101
TITLE: Long-lasting antidiabetic effect of a dipeptidyl peptidase IV-resistant **analog** of **glucagon-like peptide-1**
AUTHOR(S): Burcelin, Remy; Dolci, Wanda; Thorens, Bernard
CORPORATE SOURCE: Institute of Pharmacology and Toxicology, Lausanne, CH-1005, Switz.
SOURCE: Metab., Clin. Exp. (1999), 48(2), 252-258
CODEN: METAAJ; ISSN: 0026-0495
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glucagon-like peptide-1(7-37) (GLP-1) is the most potent insulinotropic hormone characterized thus far. Because its activity is preserved in non-insulin-dependent diabetes mellitus (NIDDM) patients, it is considered a potential new drug for the treatment of this disease. One limitation in its therapeutic use is a short half-life in vivo (5 min), due in part to a fast degrdn. by the endoprotease dipeptidylpeptidase IV (DPPIV). Recently, it was reported that GLP-1 became resistant to DPPIV when the alanine residue at position 8 was replaced by a glycine (GLP-1-Gly8). We report here that this change slightly decreased the affinity of the peptide for its receptor (IC50, 0.41.+-.0.14 and 1.39.+-.0.61 nmol/L for GLP-1 and GLP-1-Gly8, resp.) but did not change the efficiency to stimulate accumulation of intracellular cAMP (cAMP) (EC50, 0.25.+-.0.05 and 0.36.+-.0.06 nmol/L for GLP-1 and GLP-1-Gly8, resp.). Second, we demonstrate for the first time that this mutant has an improved **insulinotropic activity** compared with the wild-type peptide when tested in vivo in an animal model of diabetes. A single injection of 0.1 nmol GLP-1-Gly8 in diabetic mice fed a high-fat diet can correct fasting hyperglycemia and glucose intolerance for several hours, whereas the activity of 1 nmol GLP-1 vanishes a few minutes after injection. These actions were correlated with increased insulin and decreased glucagon levels. Interestingly, normoglycemia was maintained over a period that was longer than the predicted peptide half-life, suggesting a yet undescribed long-term effect of GLP-1-Gly8. GLP-1-Gly8 thus has a markedly improved therapeutic potential compared with GLP-1, since it can be used at much lower doses and with a more flexible schedule of administration.

IT **89750-14-1, Glucagon-like peptide I**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(glycine **derivs.**; long-lasting antidiabetic effect of a dipeptidyl peptidase IV-resistant **analog** of **glucagon-like peptide-1**)

REFERENCE COUNT: 34
REFERENCE(S):
(1) Beauvais, A; Infect Immun 1997, V65, P3042 CAPLUS
(2) Deacon, C; Diabetes 1995, V44, P1126 CAPLUS
(3) Deacon, C; Diabetologia 1998, V41, P271 CAPLUS
(5) Drucker, D; Proc Natl Acad Sci USA 1987, V84, P3434 CAPLUS
(6) Fehmann, H; Endocrinology 1992, V130, P159 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 28 OF 45 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:636574 CAPLUS
DOCUMENT NUMBER: 131:252646
TITLE: New developments in the treatment of type 1 diabetes

Searched by Barb O'Bryen, STIC 308-4291

mellitus

AUTHOR(S): Haak, Thomas
CORPORATE SOURCE: Medical Dep. I, Center Internal Medicine, Diabetes-Schulungszentrum, Johann Wolfgang Goethe-Univ., Frankfurt/Main, D-60590, Germany

SOURCE: Exp. Clin. Endocrinol. Diabetes (1999), 107(Suppl. 3), S108-S113
CODEN: ECEDFQ; ISSN: 0947-7349
PUBLISHER: Johann Ambrosius Barth
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 38 refs. is given on the new developments in the treatment and management of type-1-diabetes mellitus. Treatment of type 1 diabetes mellitus has made tremendous advances within the last decades. With concern to insulin delivery there are 2 promising new approaches. One is the intrapulmonary insulin delivery which has become feasible by the development of new inhalation devices which provide a sufficient degree of intrapulmonary drug retention. Also oral insulin delivery seems feasible when surface active substances are used to cross the mucosal membrane in the gut. Clin. research has also focussed on coatings for the insulin mols. to solve the problem raised by the proteolytic activity of the digestive system. A very new agent produced by a fungus called Pseudomassaria was demonstrated to reverse the clin. signs of diabetes mellitus in mice. The compd. diffuses through the cell membrane, binds to the inner part of the insulin receptor and activates the insulin typical biol. effects. Nowadays a variety of insulin analogs are designed and tested for their clin. use. By shifting the isoelec. point towards to a slightly acidic pH, HOE 901 ppts. at physiol. pH resulting in a const. and peakless insulin delivery. NN 304 is a 14-carbon aliph. fatty acid acylated analog that binds to serum albumin resulting in a flatter time-action profile than NPH insulin. Also rapid acting insulin analogs are or will be launched in the near future aiming to ensure an improved postprandial glucose regulation. Glucagon-like peptide-1 (GLP-1) improves metabolic control by a variety of effects, e.g. the **enhancement** of **insulin secretion** and inhibition of glucagon secretion. GLP-1 reduces food and water intake controlled by the brain, and inhibits gastric emptying. A disadvantage of GLP-1 is its very short half-life. Novel derivs. with the beneficial effects of GLP-1 but a better resistance against degrdn. were designed. In addn. substances were developed inhibiting GLP-1 degrdn. or augmenting GLP-1 release from its abundant endogenous pool. There is a variety of interesting approaches aiming to improve or ease blood glucose self-monitoring. One is the development of s.c. catheters for continuous blood glucose control. In another system reverse iontophoresis is used for sampling interstitial fluid which reflects capillary blood glucose levels. Instead of using an elec. current, a brand new system creates micropores in the skin by a laser ablation system. Through these micropores a specific device performs a mild suction to obtain interstitial fluid. Further systems which measure blood glucose by near IR spectroscopy are still investigated to improve their tech. function and to reduce their wt.

REFERENCE COUNT: 38
REFERENCE(S):
(1) Anderson, J; Drugs of Today 1998, V34, P37 CAPLUS
(4) Carino, G; Adv Drug Deliv Rev 1999, V35, P249 CAPLUS
(6) Di Marchi, R; Peptides: Chemistry and Biology 1992, P26 CAPLUS
(7) Drejer, K; Diabetes Metab Rev 1992, V8, P259 CAPLUS
(8) Drucker, D; Diabetes 1998, V47, P159 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searched by Barb O'Bryen, STIC 308-4291

L57 ANSWER 29 OF 45 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:750460 CAPLUS
DOCUMENT NUMBER: 130:76579
TITLE: Examination of somatostatin involvement in the inhibitory action of GIP, **GLP-1**, amylin and adrenomedullin on gastric acid release using a new SRIF antagonist **analog**
AUTHOR(S): Rossowski, Wojciech J.; Cheng, Beng-L.; Jiang, Ning-Y.; Coy, David H.
CORPORATE SOURCE: Peptide Research Laboratories, Department of Medicine, Tulane University School of Medicine, New Orleans, LA, 70112-2699, USA
SOURCE: Br. J. Pharmacol. (1998), 125(5), 1081-1087
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of a new type 2 selective somatostatin (SRIF) receptor antagonist (DC-41-33) on somatostatin-induced inhibition of pentagastrin-stimulated gastric acid secretion in conscious, chronic gastric fistula equipped rats was studied. Infused i.v., DC-41-33 dose-dependently inhibits SRIF-induced inhibition of pentagastrin-stimulated gastric acid secretion with an IC50 of 31.6.+-.1.2 nmol kg-1 vs. 10 nmol kg-1 SRIF and blocks the inhibitory effects of SRIF when simultaneously co-infused. Its effectiveness provides addnl. evidence that SRIF-inhibition of gastric acid release is a SRIF type 2 receptor-mediated process. DC-41-33 is able to completely reverse the inhibitory **effect** of glucose-dependent **insulinotropic** polypeptides, GIP and GIP-(1-30)NH2, and glucagon-like polypeptide, GLP-1(7-36)NH2, on pentagastrin-stimulated gastric acid secretion thus confirming that they exert these effects through stimulation of endogenous SRIF release. DC-41-33 only partially blocks potent amylin and adrenomedullin-induced inhibition of gastric acid secretion, therefore suggesting that somatostatin may not function as a primary mediator in the action of these peptides. The results indicate that DC-41-33, is a potent in vivo inhibitor of exogenous and endogenous SRIF in rats. It represents a new class of SRIF analogs which should eventually provide excellent tools for further evaluating the many physiol. roles of SRIF and its five receptor subtypes.

REFERENCE COUNT: 34
REFERENCE(S):
(1) Aurang, K; J Pharmacol Exp Ther 1997, V281, P245 CAPLUS
(2) Bass, R; Mol Pharmacol 1996, V50, P709 CAPLUS
(3) Brown, J; Recent Prog Horm Res 1975, V31, P487 CAPLUS
(4) Cooper, G; Biochim Biophys Acta 1989, V1014, P247 CAPLUS
(6) Eissele, R; Scand J Gastroenterol 1990, V25, P449 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L57 ANSWER 30 OF 45 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:261493 CAPLUS
DOCUMENT NUMBER: 120:261493
TITLE: Structure-activity relationships of glucagon-like peptide-1(7-36)amide: **insulinotropic activities** in perfused rat pancreases, and receptor binding and cyclic AMP production in RINm5F cells
AUTHOR(S): Watanabe, Y.; Kawai, K.; Ohashi, S.; Yokota, C.; Suzuki, S.; Yamashita, K.

Searched by Barb O'Bryen, STIC 308-4291

CORPORATE SOURCE: Inst. Clin. Med., Univ. Tsukuba, Tsukuba, 305, Japan
SOURCE: J. Endocrinol. (1994), 140(1), 45-52
CODEN: JOENAK; ISSN: 0022-0795
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To examine the structure-**activity** relationships in the **insulinotropic activity** of glucagon-like peptide-1(7-36) amide (GLP-1(7-36)amide), the authors synthesized 16 analogs, including eight which were designed by amino acid substitutions at positions 10 (Ala10), 15 (Ser15), 16(Tyr16), 17 (Arg17), 18 (Lys18), 21 (Gly21), 27 (Lys27) and 31 (Asp31) of GLP-1(7-36)amide with an amino acid of GH-releasing factor possessing only slight **insulinotropic activity**, and three tentative antagonists including [Glu15]-GLP-1(8-36)amide. Their **insulinotropic activities** were assessed by rat pancreas perfusion expts., and binding affinity to GLP-1 receptors and stimulation of cAMP prodn. were evaluated using cultured RINm5F cells. **Insulinotropic activity** was estd. as GLP-1(7-36)amide = Tyr16 > Lys18, Lys27 > Gly21 > Asp31 .mchgt. Ser15, Arg17 > Ala10 .mchgt. GRF > [Glu15]-GLP-1(8-36) amide. Displacement activity against 125I-labeled GLP-1(7-36)amide binding and stimulatory activity for cAMP prodn. in RINm5F cells correlated well with their **insulinotropic activity** in perfused rat pancreases. These results demonstrate that (1) positions 10 (glycine), 15 (aspartic acid) and 17 (serine) in the amino acid sequence of GLP-1(7-36)amide, in addn. to the N-terminal histidine, are essential for its **insulinotropic activity** through its binding to the receptor, (2) the amino acid sequences for the C-terminal half of GLP-1(7-36)amide also contribute to its binding to the receptor, although they are less important compared with those of the N-terminal half, and (3) [Glu15]-GLP-1(8-36) amide is not an antagonist of GLP-1(7-36)amide as opposed to des-His1 [Glu9] glucagon amide which is a potent glucagon antagonist.

L57 ANSWER 31 OF 45 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:420852 CAPLUS
DOCUMENT NUMBER: 119:20852
TITLE: Additive **insulinotropic effects** of exogenous **synthetic** human gastric inhibitory polypeptide and **glucagon-like peptide-1**-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations
AUTHOR(S): Nauck, Michael A.; Bartels, Eckart; Oerskov, Catherine; Ebert, Reinhold; Creutzfeldt, Werner
CORPORATE SOURCE: Dep. Med., Georg August Univ., Goettingen, Germany
SOURCE: J. Clin. Endocrinol. Metab. (1993), 76(4), 912-17
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1-(7-36) amide (GLP-1) are glucose-dependent insulinotropic gut hormones that may explain the greater insulin secretory response with oral compared to i.v. glucose (incretin effect). To study their individual and combined contributions, in 8 healthy volunteers, on sep. occasions, synthetic human GIP (1 pmol/kg/min) and/or GLP-1 (0.3 pmol/kg.min) or placebo were infused i.v. (-30 to 120 min), while at 0 min, a glucose infusion isoglycemic to the profile after an oral glucose load of 50 g/400 mL was started. After the administration of 50 g oral glucose, immunoreactive GIP rose several-fold to 337 pmol/L, while there was only a transient (10-30 min) and moderate increment in immunoreactive GLP-1 (from basal, 25-30, to 41 pmol/L). Isoglycemic i.v. glucose infusions led to smaller B-cell

responses (estd. incretin effect, 41%). With single infusions of GIP or GLP-1 (circulating concns., 464 and 54 pmol/L, resp.), B-cell responses were augmented compared to i.v. glucose alone and were no longer different from those after oral glucose. The combination of GIP and GLP-1 led to B-cell responses that were higher than those with either hormone alone (additive mode of cooperation). Plasma GIP concns. were similar after endogenous secretion (oral glucose) and i.v. infusion, while exogenously administered GLP-1 led to plasma levels that were maintained at an elevated level for a longer period during exogenous infusion than after stimulation by oral glucose. When in 7 volunteers, a lower dose (0.15 pmol/kg.min) of GLP-1 was infused during isoglycemic glucose infusion expts. only for the duration of elevated plasma levels in the oral glucose challenges (0-30 min), a transient, increment in insulin and C-peptide concns. was obsd., which was equiv. to 26% of the estd. incretin effect. Circulating GIP seems to make a major contribution to the incretin effect after oral glucose, and GLP-1 appears to mediate a smaller proportion. GIP and GLP-1 can interact in an additive manner in normal man.

L57 ANSWER 32 OF 45 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:16644 CAPLUS
DOCUMENT NUMBER: 118:16644
TITLE: Lack of effect of **synthetic** human gastric inhibitory polypeptide and **glucagon-like peptide 1** [7-36 amide] infused at near-physiological concentrations on pentagastrin-stimulated gastric acid secretion in normal human subjects
AUTHOR(S): Nauck, Michael A.; Bartels, Eckart; Oerskov, Cathrine; Ebert, Reinhold; Creutzfeldt, Werner
CORPORATE SOURCE: Dep. Med., Georg-August-Univ., Goettingen, Germany
SOURCE: Digestion (1992), 52(3-4), 214-21
CODEN: DIGEBW; ISSN: 0012-2823
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 [7-36 amide] (GLP-1) are glucose-dependent insulinotropic gut hormones. Under exptl. conditions, both have been shown to reduce stimulated gastric acid secretion. To study their individual and combined effects on pentagastrin-stimulated (0.1 .mu.g/kg/h from -90 to 120 min) gastric vol. and acid and chloride outputs, on sep. occasions, synthetic human GIP (1 pmol/kg/min) and/or GLP-1 [7-36 amide] (0.3 pmol/kg/min) or placebo (0.9% NaCl with 1% albumin) were infused i.v. (from -30 to 120 min) into 9 healthy volunteers. At 0 min, a glucose infusion was started that mimicked the glycemic profile after an oral glucose load of 50 g/400 mL and allowed for the glucose-dependent **insulinotropic action** of GIP and GLP-1 [7-36 amide]. Pentagastrin stimulated acid output significantly, but neither GIP nor GLP-1 [7-36 amide] either alone or in combination, reduced pentagastrin-stimulated gastric acid secretion. The circulating concns. of GIP and GLP-1 [7-36 amide] obtained at steady state during exogenous administration of synthetic peptides were similar to or higher than those reached after oral glucose (endogenous secretion). In conclusion, (penta)gastrin-stimulated gastric acid secretion is not inhibited by physiol. circulating concns. of GIP or GLP-1 [7-36 amide]. Therefore, the **insulinotropic action** of these intestinal hormones is physiol. more important than their possible role as enterogastrone.

L57 ANSWER 33 OF 45 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2001-367611 [38] WPIDS
DOC. NO. CPI: C2001-112778
TITLE: Use of milk protein hydrolysate, especially whey protein hydrolysate or caseinoglycomacropeptide for prevention and treatment of diabetes or syndrome X.
DERWENT CLASS: B04 D16
INVENTOR(S): DARIMONT-NICOLAU, C; GREMLICH, S; MACE, K; NEESER, J; REIMER, R
PATENT ASSIGNEE(S): (NEST) SOC PROD NESTLE SA
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001037850	A2	20010531	(200138)*	EN	27

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001037850	A2	WO 2000-EP10716	20001027

PRIORITY APPLN. INFO: GB 1999-27603 19991122

AB WO 200137850 A UPAB: 20010711
NOVELTY - Use of a milk protein hydrolysate or compound including a milk protein hydrolysate, which is capable of inducing release of glucagon-like peptide-1 (GLP-1), in a bioavailable form, in the manufacture of a composition for the treatment or prevention of diabetes or syndrome X, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a model for the study of proglucagon gene expression and GLP-1 production by humans, comprising cells obtained from a cell line derived from an adenocarcinoma of human caecum;

(2) assessing proglucagon gene expression and **GLP-1** release in humans comprising a cell line **derived** from an adenocarcinoma of human caecum;

(3) use of a cell line (L) derived from an adenocarcinoma of human caecum to assess proglucagon gene expression and GLP-1 release in vitro; and

(4) treatment or prevention of diabetes or syndrome X which comprises administering an effective amount of a milk protein hydrolysate which is capable of inducing release of GLP-1.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - GLP-1 release inducer. The release of GLP-1 in human NCI-H716 intestinal cells stimulated by CGMP was studied. NCI-H716 (1 multiply 106) cells were seeded in 12 well culture plates containing BSA (bovine serum albumin) with or without CGMP. Cells were incubated for 2 hours at 37 deg. C. The amount of GLP-1 released in the medium after 2 hours incubation period with increase in concentrations (0.25-2.5 mg/ml weight/volume) of the calcium form of CGMP was evaluated. CGMP induced a dose-dependent increase in GLP-1 concentrations with maximum secretion reaching 259 plus or minus 77% of the control values with 2.5 mg/ml of CGMP-Ca. When stimulated with sweet and acid whey (5 mg/ml) an increase in

GLP-1 release of 298 plus or minus 34% and a 284 plus or minus 21%, respectively compared to control condition was observed. Another protein hydrolysate, meat hydrolysate, did not induce such an effect on GLP-1 production, at 5 mg/ml.

USE - The milk protein hydrolysate or compound including the hydrolysate is useful for treating or preventing diabetes or syndrome X (claimed).

ADVANTAGE - The composition reduces the risk of hypoglycemic reactions. The action of GLP-1 is glucose dependent and eliminates the risk of hypoglycemia, i.e. the release of insulin is very fine-tuned with respect to the blood glucose levels. GLP-1 remains active in persons with diabetes, whereas the other incretin hormone, glucose dependent **insulinotropic** peptide loses **effectiveness** in diabetes. Conventional treatment raises insulin levels, but the milk protein hydrolysate composition increases insulin mRNA, beta-cell sensitivity and lowers glucagon levels. The composition regulates appetite and reduces food intake. The oral treatment method is safer and more convenient for patients than conventional treatment by injection.

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L57 ANSWER 34 OF 45 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-080751 [09] WPIDS
DOC. NO. CPI: C2001-023296
TITLE: Synergistic use of thiazolidinediones with glucagon-like peptide for treating non-insulin dependent diabetes mellitus.
DERWENT CLASS: B04 B05
INVENTOR(S): JOHNSON, W T; STRAMM, L E; VIGNATI, L; YAKUBU-MADUS, F E
PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000078333	A2	20001228	(200109)*	EN	24

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000053252 A 20010109 (200122)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000078333	A2	WO 2000-US15548	20000606
AU 2000053252	A	AU 2000-53252	20000606

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000053252	A Based on	WO 200078333

PRIORITY APPLN. INFO: US 1999-139794 19990621

AB WO 200078333 A UPAB: 20010213
NOVELTY - Treating non-insulin dependent diabetes mellitus (NIDDM), comprising co-administering an incretin hormone (I) and thiazolidinedione (II), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an insulinotropic formulation comprising (I) and (II); and

(2) a composition (C) comprising a container suitable for holding a solution to be infused in a patient, a liquid preparation comprising (I) for administration at a dosage of 20-200 micro g/day, and instructions on infusing a patient suffering from NIDDM, with the preparation, so that the patients blood glucose level is decreased and **insulin secretion** is **increased.**

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - Decreases blood glucose level and **increases insulin secretion** (claimed).

TZD 300512 was administered as 0.00006 % diet admixture to eight week old Zucker Diabetic Fatty rats (ZDF), while IP7-GLP-1 (7-37)OH, a GLP-1 agonist, was infused subcutaneously at a constant rate of 0.06 micro g/minute through implanted Aztet pumps. The study was carried for seven weeks, and food consumption and body weight were monitored daily. Plasma glucose and insulin levels were measured weekly, and glycated hemoglobin A1c was measured at the end of the study. Heart weights also were measured at the end of the study. The data demonstrated enhanced glucose control in the ZDF rat with co-administration of suboptimal doses of IP7 and TZD without causing heart hypertrophy. The result also demonstrated enhanced glycemic control without an increase in the heart size at sub-optimal doses of TZD and GLP-1 agonist combination therapy.

USE - (I) and (II) are useful for treating NIDDM (claimed).

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